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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/381,497	02/17/2000	DAVID J. FITZGERALD	015280-317100US	4036

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JOHN STORELLA
TOWNSEND AND TOWNSEND AND CREW
TWO EMBARCADERO CENTER
8TH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
TUNGATURTHI, PARITHOSH K	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 10/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/381,497	FITZGERALD ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-11,13,14,16,17,22-26,29-32 and 50-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-11,13,14,16,17,22-26,29-32 and 50-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claim 50 has been amended.

Claim 56 has been newly added.

Claims 1-4, 7-11, 13-14, 16-17, 22-26, 29-32 and 50-56 are under examination.

2. The text of those sections of title 35, USC Code not included on the Office Action can be found in a prior Office Action.

Response to Arguments

3. The rejection of claims 50-55 and newly added claim 56 under 35 U.S.C. 112, first paragraph is maintained. The response filed on 08/26/2005 has been carefully considered but is deemed not to be persuasive. The response states that although the Applicant's disagree with the rejection, in order to expedite prosecution, claim 50 has been amended to recite that the sequences have the CDRs of SEQ ID NOs:2 and 4 (page 8 3rd paragraph).

In response to the above statement, the applicant is reminded the basis of the rejection in the non-final office action mailed on 05/23/2005. In the previous office action, the examiner has stated that while the specification is enabled for a recombinant immunotoxin comprising SEQ ID NO:2 and 4 and a cysteine at position 100 and 44, does not reasonably provide enablement for a recombinant immunotoxin comprising a sequence that is 95% identical to SEQ ID NO:2 and 4 and a cysteine at position 100 and 44 wherein the immunotoxin binds CD22 with greater than 90% affinity of the prototype RFB4 dsFv and comprises a toxin of PE38 and an expression cassette and

host cell comprising DNA encoding such immunotoxin. The rejection was based on the reasonings that the specification is not enabled for any amino acid sequence that is 95% identical to the CDRs of SEQ ID NOs:2 and 4 because the of unpredictability of the art as cited in the previous office action.

As mentioned in the previous office action, it is well established in the art that the amino acid sequences and conformations of each of the heavy and light chain CDRS are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRS in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRS, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. also teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Thus, by merely changing the sequence identity of CDRs from 95% to 90% does not significantly change the claim and hence does not overcome the unpredictable nature of the art, and thus does not render the invention allowable. In addition, Colman (Research in Immunology 145:33-36, 1994) teach that in antibody-antigen binding interactions the above examples paint a confusing picture because even a very conservative substitution may abolish binding

(see page 35). Therefore, one skill in the art would not conclude that an antibody that contained 95% identical to SEQ ID NO:2 or 4 with alterations in the CDRS would have the required binding specificity.

4. The rejection of claims 1-4, 7-11, 13-14, 16-17, 22-26, 29-32, 50-55 and newly added claim 56 under 35 U.S.C. 103(a) as being unpatentable over Ghetie et al (Cancer Res. 51:5876-5880, 1991) and further in view of Shen et al (Int. J. Cancer 42:792-797, 1988) and Reiter et al (Biochemistry 33:5451-5459, 1994) and Kuan et al (Biochemistry 35:2872-2877, 1996, Abstract published 2/1/96) and Orlandi et al (Proc. Natl. Acad. Sci. USA, 86:3833-3837, 1989), Cabilly et al (U.S Patent 4816567, issued 3/89), Boss et al (U.S Patent 4816397, issued 3/89), Robinson et al (U.S. Patent 5618920, filed 4/94), Ward et al (Nature 341:544-546, 1989), and Huston et al (U.S. Patent 5258498, issued 11/93) is maintained.

The response filed 3/4/05 has been carefully considered but is deemed not to be persuasive. The response states that the knowledge of general methods does not render any particular sequence obvious; and that the "RFB4" by Shen et al provides no structural information regarding the identity of the antibody and even if one assumes that the hybridoma was the same as that used here, one of skill would not be able to make the claimed sequences based on the combination of references cited by the examiner.

In response to this argument, the applicant is again reminded that the art cited in the previous office actions for PCR does demonstrate that it is routine in the art to

obtain the DNA and amino acid sequence of the VH and VL of any hybridoma contrary to In re Deuel. In In re Deuel the specific facts are different from those of an antibody hybridoma. While it may be unobvious to obtain just any DNA from a particular cell, the obtaining of the DNA sequence from a hybridoma for the VH and VL is routinely done as evidenced from the prior art. In addition, since Shan et al specifically teach the hybridoma cell line of RFB4 and cites Campana et al for the culturing of the cell line, and since the inventors own work describing the invention, states that the RFB4 IgG-producing hybridoma was from the Royal Free Hospital in London (see page 2020 last 2 lines of right column), one skill in the art would conclude that the hybridomas were the same. As per Shen et al not providing any structural information regarding the identity of the antibody, the studies performed by Shen et al were to compare the cytotoxic effects of a panel of IT's constructed from 4 different CD22 Mabs and their Fab' fragments and the antibodies used were RFB4, UV22-1 and UV22-2. Shen et al did not proceed on to analyzing the sequence of the antibody. However, it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the antibody RFB4 and obtain the DNA and protein sequence of the VH and the VL from the RFB4 hybridoma as taught by Shen et al by the method of Orlandi et al, Cabilly et al, Boss et al, Robinson et al, Ward et al and Huston et al as described in the previous office actions. Thus, It is the examiners position that the hybridoma and the antibody taught by Shen et al, if were analyzed for the amino acid sequence of the CDR would result in the CDRs as claimed unless otherwise the applicant can provide any evidence that the antibody "RFB4" of Shen et al is indeed

different in its amino acid sequence of CDRs from the "RFB4" antibody of the claimed invention.

The response further states that there is no reasoning or evidence in the rejection as to why one skill would conclude that RFB4 antibody-toxin conjugates claimed here would in fact have these properties, and further that the mere teaching that a composition could possibly have a characteristic does not lead to the logical conclusion that all of such compositions would have that characteristic, and that Dr. Fitzgerald explains that typically binding affinity is lowered in such a conjugate in comparison to the parent antibody (see page 7 of response). The response furthermore states that the examiner provides no evidence or reasoning as to why one skill would predict such superior properties based on the cited art.

In response to the above argument, the applicant is reminded that under 35 U.S.C. 103 it is only necessary to establish motivation to combine the references, and that the ordinary skilled artisan would have reasonable expectation of success being able to produce the invention. Applicant's arguments are not found persuasive that, assuming unpredictability in combining the cited references to produce a recombinant immunoconjugate, comprising a therapeutic agent or a detectable label covalently linked to RFB4 dsFv. As stated in the previous office action Shan et al teach hybridoma cell line of RFB4, Reiter et al (Biochemistry) teach that they have optimized the design and the purification scheme so the yields of dsFv-active immunotoxins are consistently higher than those of the scFv-toxins and the increased yield is due to the decreased

tendency of properly folded immunotoxins to aggregate (see abstract). Thus, it would not have been surprising to get higher expression or production of the dsFv-toxins. In addition, Reiter et al (Nature Biotech cited by applicant) teach 4 out of 8 dsFv-immunotoxins had improved binding affinity (see page 1243, left column). The Reiter et al (Biochemistry) clearly shows better cytotoxicity for the dsFv as compared to the scFv and better expression yields (see Table 1) and better stability (see Table 2) and teach "that dsFv's have at least the same binding properties as scFv's, and in some cases they may be better" (see abstract) and Reiter et al teach that scFv can retain the specificity and affinity of IgG (see page 5451). In addition, because the dsFv have superior characteristics over the scFv they would obviously be chosen over scFv and in addition Shen et al teach that the Fab'-RFB4 bound 1 .2 to 3.5 times more stronger than other Fab' fragments and the potent cytotoxic activity of the RFBM-AS appears to derive from their superior binding affinity and the art recognizes the superiority of this antibody. With regard to the Krietman et al reference, this reference demonstrates only one instant where the dsFv had low activity, however, in all of Reiter et al (Biochemistry) and Kuan et al (Biochemistry) the dsFv were active and potent and as such one skill in the are would have a reasonable expectation of success in making the claimed immunoconjugate dsFv with the RFB4 antibody. The decleration of Dr. Fitzgerald is respectfully considered, however it does not satisfy the unobviousness or the unpredictability of the claimed invention as stated by the applicant because the specific antibody including the further limitations as claimed are clearly known in the art. Therefore, one of skill in the art would have been motivated to and had a reasonable

expectation of success to have used the antibody RFB4 and obtain the DNA and protein sequence of the VH and the VL from the RFB4 hybridoma and use the method of Reiter et al and Kuan et al to produce a disulfide stabilized anti-CD22 antibody conjugate because Kuan et al teach immunotoxins comprising a disulfide stabilized VH and VL wherein the VH is linked to the amino terminus of the PE38 and have compared the stability of three different single-chain and dsFv inmmunotoxins wherein all three dsFv immunotoxins were more stable.

Conclusion

5. No claims are allowed.

6. **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is ~~703-872-9306.~~ 571 273-8300.

8. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi Ph.D.
(571) 272-8789

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER